Chronic Beryllium Disease: Structural, Spectroscopic, and Reactive Properties of Aqueous Beryllium Ion

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Beryllium (Be) is used in industry in metal, oxide, and alloy forms for manufacturing nuclear components, electronic devices, golf clubs, aircraft brakes, x-ray tubes, high temperature ceramics, and structural components in satellites and space shuttles. It also is listed as a Class A environmental protection agency (EPA) carcinogen and causes chronic beryllium disease (CBD), a human granulomatous lung disease. The molecular aspects of beryllium chemistry in the context of biological systems are not well understood. The ability to accurately calculate Be^{2+} coordination environments using molecular dynamics (MD) is a crucial step in being able to predict beryllium binding in proteins of interest.

Due to its small size and divalent character, the Be^{2+} ion presents a difficult challenge for representing its interactions, classically in an aqueous solution. The charge transfer from water molecules to Be^{2+} in this complex, and the interaction with water, may exhibit substantial covalent character. In the past, three-body potentials have been shown to be necessary for obtaining the correct coordination numbers of aqueous Be^{2+}. In this vein, we have recently developed a new, simple two-body potential for Be^{2+} that has ab-initio-derived Lennard-Jones parameters and a +2 charge.

This new two-body potential captures several structural, reactive, and spectroscopic properties of the Be^{2+} ion complex in water. It reproduces the correct radial distribution function and coordination numbers for this cation when compared with published diffraction and nuclear magnetic resonance (NMR) measurements. It also produces a well-established hydrogen bonding between the first and second solvation shells and yields a tetrahedral four-coordinate $[Be(H_2O)_4]^{2+}$ species. When both molecular dynamics and ab-initio results are analyzed together, the role of the solvent in the reactivity of the $[Be(H_2O)_4]^{2+}$ dication is clarified. Namely, the solvent acts to accept protons from the beryllium dication at higher pH values (>3.6). The high reactivity of the resulting $[Be(H_2O)_3(OH)]^{+}$ species then drives the formation of beryllium hydroxo clusters, such as $[Be_2(OH)_3]+$, $[Be_3(OH)_3]^{3+}$, $[Be_5(OH)_6]^{4+}$ and $[Be_6(OH)_8]^{2+}$. Moreover, an ab-initio calculation on a snapshot of the MD calculation gives the best vibration mode energies of aqueous beryllium to date.

Currently, comparative MD studies are being carried out to elucidate the differences between disease and non-disease alleles that could shed much needed microscopic insight on the roles of conformational flexibility and water on binding to Be^{2+}. Preliminary results reveal that that the effect due to K69E mutation in the disease allele is non-local and cooperative. We also identify potential binding sites and interactions of carboxyl triads that can be exploited for allele-specific genotyping. Details of force field development can be found in [1].

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[1] S. Gnanakaran et al., *J. Phys. Chem. B*, in press (2008).

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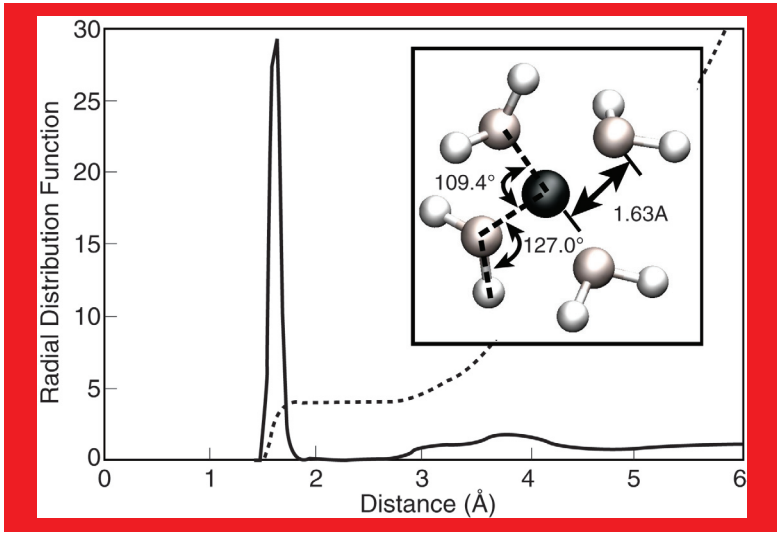

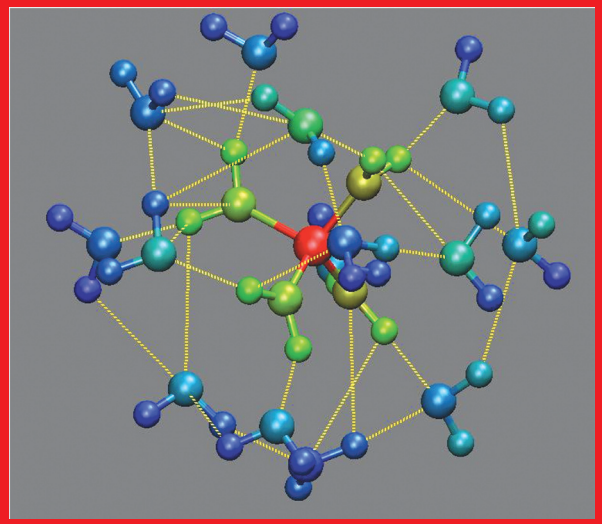

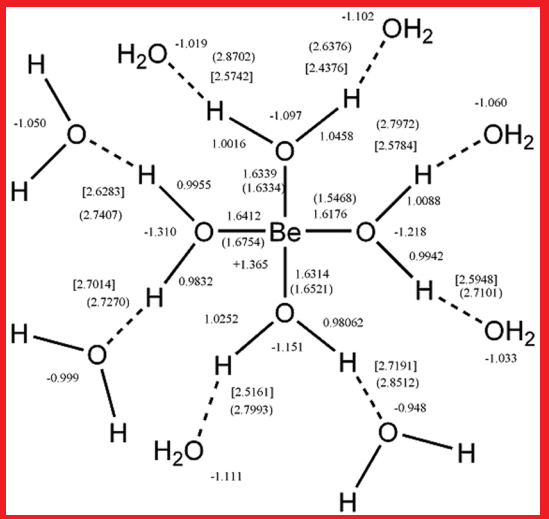

Fig. 1. **Top:** *Structural characteristics of the hydrated beryllium complex, $[Be(H_2O)_4]^{2+}$. The beryllium ion-water oxygen radial distribution function (solid) and the corresponding integration numbers (dashed) are shown. Insert: Geometric values of $[Be(H_2O)_4]^{2+}$ complex. Bond and angular values are marked.* **Bottom-left:** *Interplay between first and second solvent shells. Hydrogen bonding network between first and second shell water molecules. The Be dication is in red. The color gradient from green to blue is used to mark the distance from the cation (green:close and blue:far).* **Bottom-right:** *Influence of second solvent shell on the geometry and charge distribution of the $[Be(H_2O)_4]^{2+}$ complex. The figure provides results from ab-initio calculations. The numbers in the brackets are O-O distances and the numbers in parenthesis correspond to distances from a configuration obtained from MD.*